Maintenance therapy in Crohn’s disease

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Despite significant advances in the understanding of the mechanisms of chronic inflammation of the gastrointestinal tract, the long term control of Crohn’s disease remains a challenge for patients and their physicians. Crohn’s disease follows several modes of disease activity based on its natural history. An individual may have acute relapsing Crohn’s disease, chronically active Crohn’s disease or quiescent Crohn’s disease. This somewhat artificial division may

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Crohn’s disease is in clinical remission as defined by conventional clinical criteria. Although successful maintenance therapy may appear to prolong clinical remission, in the majority of patients it may simply provide ongoing, active treatment of the residual endoscopic and histological disease activity. Whether maintenance therapy beneficially alters the overall natural history of the disease is not known, despite the fact that some maintenance therapies appear to reduce the risk of clinical relapse or prolong the duration of clinical remission. Ideally, the goals of any successful maintenance therapy should include some or all of the following aspects: reduction in the frequency and severity of recurrent symptoms, maintenance of optimal nutritional status, avoidance of disease- and treatment-related complications, healing of the intestinal mucosa and maintenance of optimal health-related quality of life (Table 1).

**CONVENTIONAL GLUCOCORTICOIDs**

Conventional glucocorticoids such as prednisone, prednisolone and methylprednisolone have been shown to be highly effective in treating the acute symptoms of Crohn’s disease flares (5,8,9). Remission can be achieved with a course of oral glucocorticoids in 60% to 92% of patients, but for the majority of patients, continuous low dose glucocorticoid therapy does not improve clinical remission rates over one to two years (5,8,11,12). However, closer evaluation of the results of the European and National Cooperative Crohn’s Disease Studies (5,8) suggests that there may be a subset of patients with Crohn’s disease who, after responding to an initial course of high dose glucocorticoid therapy, are more likely to remain in remission if the glucocorticoid therapy is continued at a low dose. Chronic glucocorticoid therapy can result in significant cosmetic, psychiatric, metabolic and bone-related side effects and complications, and its use over extended periods of time has generally been disfavoured by many physicians and not accepted by patients (13). Nevertheless, in a few patients, the use of low dose glucocorticoids can be considered. Typically, this would be a patient in whom multiple attempts at glucocorticoid weaning have been unsuccessful, in whom a relatively low dose of prednisone (10 to 15 mg/day) adequately controls disease symptoms and in whom there are no significant adverse effects at
the dose required to control symptoms. Other steroid-sparing strategies should have been tried or offered to the patient before embarking on chronic glucocorticoid therapy. If chronic glucocorticoid therapy is used, careful monitoring for long term sequelae is mandatory.

**BUDESONIDE**

The controlled ileal release form of budesonide, an effective form of therapy for active Crohn’s disease, was evaluated as a potential and safer maintenance therapy than conventional glucocorticoids. Unfortunately, the results of clinical trials have not been impressive (3,4,14). Although the safety profile of budesonide 3 and 6 mg/day was quite favourable, only the 6 mg/day dose was able to marginally prolong the mean time until relapse, and it provided no overall remission maintenance advantage after one year of therapy. It is not known whether chronic, continuous therapy with the higher active dosage of budesonide (9 mg/day) is effective or safe. However, a dosage of 9 mg/day demonstrates evidence of a systemic glucocorticoid effect based on the appearance of a measurable inhibition of adrenal responsiveness (15). In patients whose acute symptoms of Crohn’s disease respond to budesonide 9 mg/day, it seems reasonable to maintain them on a dosage of 6 mg/day. However, physicians should be ready to increase the dosage to 9 mg/day if disease symptoms recur.

**MESALAZINE (5-AMINOSALICYLATES)**

Although mesalazine’s good tolerability and excellent safety record make it an attractive choice for long term maintenance therapy, its efficacy in maintaining remission in Crohn’s disease is, at best, questionable. Some clinical trials have suggested that mesalazine may be effective in certain subgroups of patients (eg, those in remission for only a short period of time), while others have shown that, overall, the treatment effect observed with mesalazine in patients with medically induced remission is minimal and not statistically significant (16-26). In patients who required glucocorticoids to control acute symptoms of Crohn’s disease, mesalazine 4 g/day appeared to offer no therapeutic advantage over placebo (6).

**AZATHIOPRINE AND 6-MERCAPTOPURINE**

Immunomodulatory drugs are becoming increasingly popular as maintenance therapies for patients with Crohn’s disease. Long term safety data are accumulating for these drugs, and efficacy has been consistently seen in clinical trials (2,27-29). Although all of the trials of azathioprine and 6-mercaptopurine have suffered from significant methodological deficiencies, there is sufficient consistency among the results to suggest that there is likely a true treatment effect. In a meta-analysis of five placebo controlled trials of azathioprine maintenance therapy involving 319 patients, Pearson and colleagues (30) calculated an odds ratio of 2.19 for maintenance of remission in patients receiving azathioprine. This demonstration of effectiveness is strengthened by the dose response that was observed in the meta-analysis. Preliminary evidence suggests that 6-mercaptopurine, the active metabolite of azathioprine, may reduce the risk of endoscopic and clinical relapse after surgical resection for Crohn’s disease (31).

**METHOTREXATE**

Methotrexate is effective in the treatment of patients with chronically active, steroid-dependent Crohn’s disease when given as weekly intramuscular injections of 25 mg (32). Although many physicians find that patients who respond acutely to methotrexate appear to do well when the drug is continued as maintenance therapy, there has been no controlled trial evidence to support this impression until recently. The results of the follow-up maintenance phase of the North American Crohn’s Study Group methotrexate trial (33) confirm the clinical impression of many physicians. In the maintenance study, weekly intramuscular injections of 15 mg of methotrexate were compared with placebo injections in patients who had responded to an initial acute course of methotrexate. Sixty-five per cent of the methotrexate-treated patients maintained remission over the 48-week study period, compared with 39% of the placebo-treated patients. The steroid-sparing effect was even more significant. No additional steroid therapy was required in 72% of the methotrexate-treated patients, but only 42% of the placebo-treated patients remained steroid-free. Methotrexate appeared to be well tolerated at the 15 mg maintenance dose and was not associated with significant toxicity. Given these results, the frequency of use of methotrexate as maintenance therapy for Crohn’s disease is likely to increase in the near future.

**ANTIBIOTICS**

The role of antibiotics in the management of Crohn’s disease is controversial. Antibiotics are used by many physicians, particularly to treat acute septic complications of Crohn’s disease. However, the evidence supporting the effectiveness of antibiotics – in most studies metronidazole – in ameliorating the symptoms of acute disease activity is not conclusive (34-37). There have been no controlled trials of antibiotics for the maintenance of medically induced remissions.

In an open series, 72 patients were treated with a combination of ciprofloxacin and metronidazole for symptoms of active Crohn’s disease (38). Of the 55 patients who responded, 15 were maintained on chronic combination antibiotic therapy for a mean follow-up of nine months. Of these 15 patients, 12 (80%) remained in remission for the duration of follow-up. In comparison, 26 of 40 (65%) patients who elected to stop antibiotics remained in remission. Rutgeerts et al (39) examined the role of antibiotics in preventing or delaying the appearance of postoperative endoscopic and clinical recurrence. They found that metronidazole 20 mg/kg daily for three months after resection reduced the severity of recurrent endoscopic lesions and appeared to reduce or delay clinical recurrence, although the latter did not achieve statistical significance. These results are suggestive, and further studies examining alternative antibiotics, dosing schedules and duration of therapy need to be conducted.
The importance of tumour necrosis factor (TNF) in the pathogenesis of intestinal inflammation in Crohn’s disease is shown by the high response rate seen when the human-mouse chimeric anti-TNF antibody, known as infliximab (Remicade, Centocor, USA) is used to treat patients who are not responsive to conventional therapies (40,41). Response rates of up to 81% were seen with a single intravenous infusion of 5 mg/kg in patients with intestinal disease activity. Up to 68% of patients with fistulizing Crohn’s disease responded to three infusions of infliximab 5 mg/kg. Remission or complete responses were seen in 48% and 55% of patients with intestinal disease activity and fistulizing disease, respectively. Improvements in endoscopic disease activity, particularly in the right colon and rectum, were observed in a subset of patients (42). No maintenance data are available for patients with fistulizing disease activity and fistulizing disease, respectively. Improvements in endoscopic disease activity, particularly in the right colon and rectum, were observed in a subset of patients (42). No maintenance data are available for patients with fistulizing disease activity and fistulizing disease, respectively. Improvements in endoscopic disease activity, particularly in the right colon and rectum, were observed in a subset of patients (42).

For patients with intestinal disease activity, repeated infusions of infliximab, given every eight weeks, maintain the improvement observed after one or two initial infusions (7). In the retreatment study, 73 patients who had responded to an initial infusion of infliximab received either infliximab 10 mg/kg or placebo infusions beginning 12 weeks after the initial infusion for active disease. Four additional infusions of infliximab or placebo were given at eight-week intervals, and patients were followed-up for 10 weeks after the final infusion. Infliximab improved disease activity when assessed by CDAI scores, disease-related quality-of-life scores and serum C-reactive protein concentrations. In addition, the proportion of patients in remission increased from 37.8% at the start of retreatment to 60% during the retreatment phase. In those who received placebo infusions, the proportion in remission fell from 44.4% before retreatment to 35% during retreatment (Figure 2).

Many issues need to be settled regarding the role and appropriate use of infliximab for maintenance therapy in patients with Crohn’s disease. The optimal dose has not been determined. Unfortunately, only the 10 mg/kg dose was studied in the retreatment trial; this dose was different from the 5 mg/kg dose that was found to be most effective in the acute trials, and for which the drug currently is indicated for use in the United States and Europe. It is not known whether the 5 mg/kg dose is as effective as – or perhaps, more effective than – the 10 mg/kg dose. It is important to know whether retreatment needs to be given every eight weeks or whether it can be given ‘on demand’ according to patients’ symptoms, and also whether retreatment needs to be continued beyond the four doses reported by Rutgeerts et al (7).
The efficacy of infliximab maintenance therapy in patients with healed fistulae is also unknown.

Because of infliximab’s high cost, patients, third-party payers and society will be interested in its cost effectiveness relative to existing medical and surgical therapies. Economic analyses have suggested that the major determinant of total cost of health care for patients with Crohn’s disease is inpatient costs (43,44). The cost of infliximab may be offset by the savings realized through reductions in hospital and surgical care.

Although experience with the use of infliximab is accumulating, concerns regarding its long term safety remain. Lymphoma has been reported in patients treated with infliximab. In the retreatment trial by Rutgeerts et al (7), one patient who was treated with a single initial infusion of infliximab and placebo retreatments developed a B-cell lymphoma 9.5 months after the initial infusion. In a much larger retreatment study of infliximab in 428 patients with rheumatoid arthritis, one B-cell lymphoma, one recurrent breast cancer and one melanoma were observed in infliximab-treated patients (45). The observed number of malignancies was calculated to be the same as the expected number based on an age- and sex-matched cohort of the general population. Notwithstanding this conclusion, the long term safety of infliximab remains to be more definitively established. Ongoing monitoring and postmarketing surveillance are required to gain a better understanding of the chronic or intermittent use of infliximab.

Another issue that needs to be studied further is the role of cotherapy with other immunomodulatory drugs. There is evidence from patients with infliximab-treated rheumatoid arthritis that the concomitant administration of methotrexate can reduce the immunogenicity of infliximab and improve efficacy (46,47). Some of these issues should be addressed by studies currently in progress or by those planned for the near future.

A second anti-TNF antibody, CDP571, is a humanized monoclonal antibody currently in development for the treatment of Crohn’s disease. A large clinical trial has shown its efficacy in patients with Crohn’s disease refractory to other therapies (48). In that study, two or three infusions of the antibody were better than placebo infusions at achieving and maintaining clinical improvement over 24 weeks. A smaller, short term maintenance study involving 71 patients in remission on steroid therapy was also reported (49). Patients were randomly assigned to receive either placebo infusions or CDP571 20 mg/kg at week 0 and 10 mg/kg at week 8. Steroid doses were tapered by week 10 and patients were followed-up for 16 weeks. Twenty-two per cent of the placebo-treated patients remained in remission at the end of follow-up, compared with 44% of the CDP571-treated patients.

**SUMMARY**

Several options are available for maintenance therapy of Crohn’s disease (Table 2). The choice of which therapy to use in an individual patient should depend on the disease complications, the patient’s previous response to therapy, the relative long term safety record of the available choices, the relative therapy efficacy and cost. In the absence of direct comparative data among the various choices, physicians and patients must make decisions based on the available evidence in the literature, and on personal preference and experience.

**TABLE 2**

Possible maintenance therapies for Crohn’s disease with ratings of the strength of the evidence in support of their use and the strength of the treatment effect observed in clinical trials

<table>
<thead>
<tr>
<th>Maintenance therapy</th>
<th>Strength of evidence and effect</th>
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<tbody>
<tr>
<td>Conventional glucocorticoids</td>
<td>+/-</td>
</tr>
<tr>
<td>Budesonide</td>
<td>+</td>
</tr>
<tr>
<td>Mesalazine</td>
<td>+/-</td>
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<tr>
<td>Azathioprine and 6-mercaptopurine</td>
<td>++</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>++</td>
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<tr>
<td>Antibiotics</td>
<td>-</td>
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<tr>
<td>Infliximab</td>
<td>++</td>
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</tbody>
</table>

- No evidence of treatment effect or evidence of no effect; +/- Questionable evidence of treatment effect; + Fair evidence of treatment effect or evidence of only modest effect; ++ Good evidence of treatment effect

REFERENCES
